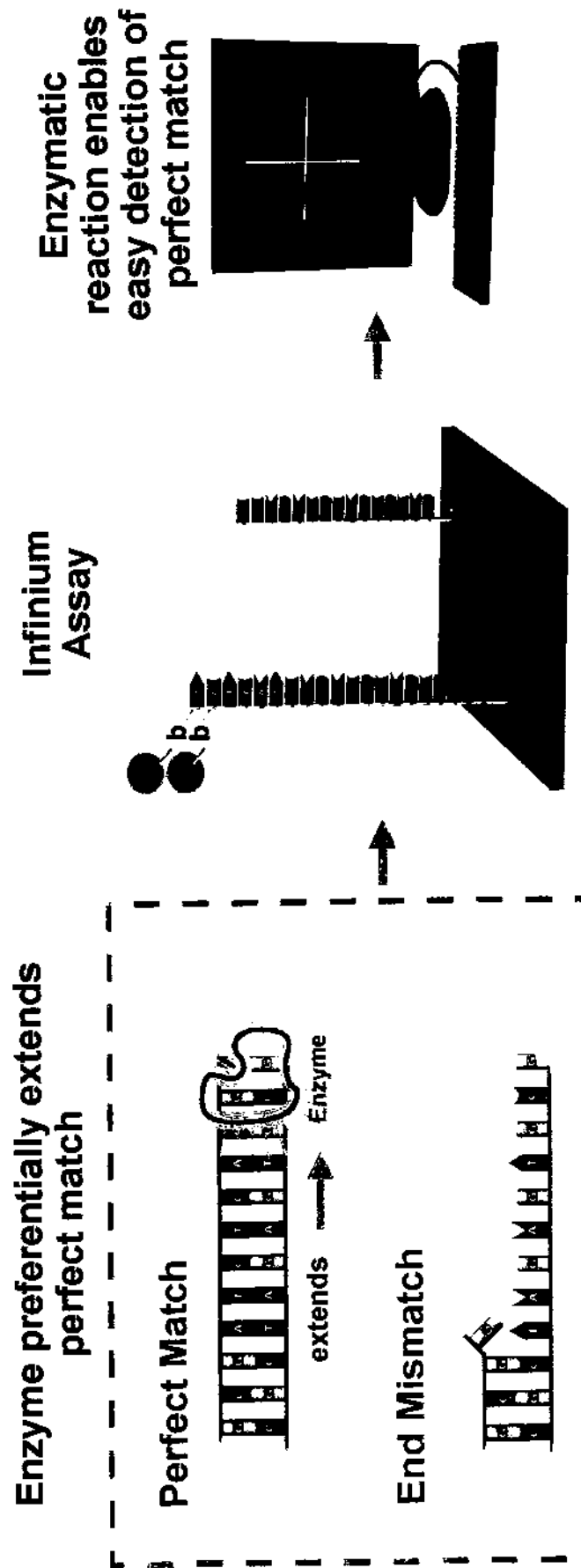


# Infinium indicates the extent of enzymatic reaction



# Infinium indicates the extent of enzymatic reaction



# '716 patent requires a base call by a "comparison of said plurality of probe intensities to each other"

## '716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison and **\_\_\_\_\_**; and

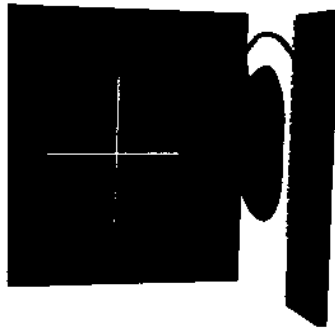
a computer readable medium that stores said computer codes.

'716 Patent col. 41:59-67; 42:59-67

## Court's Construction

13. The phrase "comparison of said plurality of probe intensities to each other," as used in the claims of U.S. Patent No. 5,795,716, means "an examination of the probe intensities of two or more probes in relation to each other;"

Markman Order at ¶ 13



Base call made by a comparison of probe intensities to each other

Base call made according to sequence of nucleic acid probe (i.e., probe at probe location)

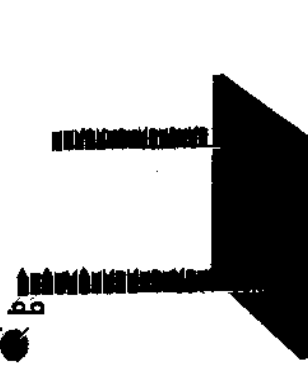
# Illumina's Assays And GenCall Are Substantially Different From '716 Patent Claims

Illumina's Assays/GenCall		'716 Patent
Equivalence	Enzymatic Assay	Hybridization-only
Function	Enzyme + Labeling of probe	Labeled Sample Nucleic Acid + Strength of binding
	More accurate genotype calls	Inaccurate base calls
Way		
Result		

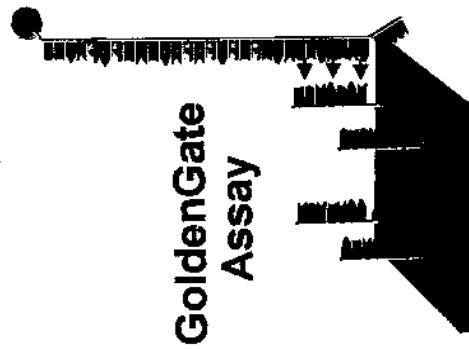
**NOT EQUIVALENT -- Why?  
Enzymes, Tags, and GenCall**

# GenCall makes calls based on clustering with training data, *not* "comparison of intensities to each other"

Infinium Assay

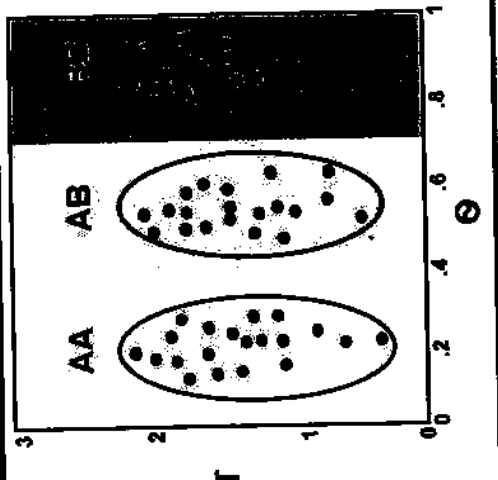


Transformation  
& Clustering



GoldenGate  
Assay

CLUSTERING WITH TRAINING DATA



## Court's Construction

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

APPROPRIATE, INC.,  
Plaintiff,

v.  
TRIADINA, INC.,  
Defendant.

Civil Action No. 04-001 277

13. The phrase "comparison of said plurality of probe intensities to each other," as used in the claims of U.S. Patent No. 5,795,716, means "an examination of the probe intensities of two or more probes in relation to each other."

Markman Order at ¶ 13

3. The term "substrate," as used in the claims of U.S. Patent No. 5,441,343, means "a material having a rigid or semi-rigid surface."

# '716 Patent Does Not Cover Enzyme-Based Assays Or Tags

## '716 File History

or the Maxam and Gilbert method. More specifically, Weiss describes utilizing an enzyme on identical probes that hybridize with tags in the fragments of the nucleic acid ladder. The

Weiss and Stockham do not disclose or suggest inputting probe intensities to identify an unknown base where the probe intensities indicate the extent of hybridization of probes differing by a single base and the sample nucleic acid sequence.

In stark contrast, the present invention compares probe intensities that indicate the extent of hybridization of probes differing by a single base and the sample nucleic acid sequence.

IAFP00000402-403

Illumina's assays use  
*enzymes and tags*



They are in  
"stark contrast" to  
the invention of the  
'716 patent

# Illumina's products do not infringe the '716 patent

Asserted Claims	GoldenGate-GenCall	Infinium-GenCall
Claim 1	<ul style="list-style-type: none"> <li>- No probe intensity</li> <li>- No intensity indicating relative strength of binding</li> </ul>	<ul style="list-style-type: none"> <li>- No probe intensity</li> <li>- No intensity indicating relative strength of binding</li> </ul>
Claim 5	<ul style="list-style-type: none"> <li>- No base call based on comparison of probe intensities to each other</li> </ul>	<ul style="list-style-type: none"> <li>- No base call based on comparison of probe intensities to each other</li> </ul>
Claim 9	<ul style="list-style-type: none"> <li>- No array of probes</li> </ul>	

**NO INFRINGEMENT -- Why?  
Enzymes, Tags, and GenCall**

# '531 Claims Require Making A "Biological Chip Plate"

## '531 Patent Claim 1

1. A method for making a biological chip plate comprising the steps of:
  - (a) providing a body comprising a plurality of wells defining spaces;
  - (b) providing a wafer comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner;
  - (c) attaching the wafer to the body so that the probe arrays are exposed to the spaces of the wells.

Claim 1, '531 Patent, col. 12:40-51

## '531 Patent Specification

D. ~~Device~~ A collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner.

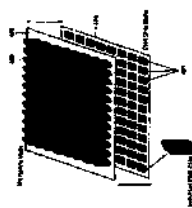
E. Biological Chip: A substrate having a surface to which one or more ~~arrays~~ of probes is attached....

\* \* \*

G. Biological Chip Plate: A device having an array of biological chips in which the probe array of each chip

'531 Patent col. 4:1-25

United States Patent  
 6,443,234  
 Issued to: ~~David A. H. Jones~~  
 Filed: ~~Aug. 15, 2000~~  
 Title: ~~Biological Chip Plate~~  
 Abstract: ~~A biological chip plate is disclosed. The plate includes a body having a plurality of wells defining spaces. A wafer is attached to the body so that the probe arrays are exposed to the spaces of the wells. The wafer includes a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner.~~





# Illumina Does Not Infringe the '531 Patent

## Asserted Claims

### Claim 1

### Claim 2

## Accused Methods

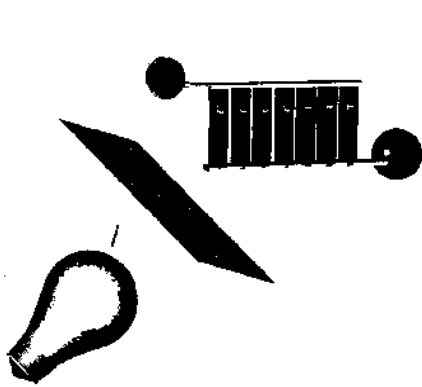
- No "... making a biological chip plate"
- No "providing a wafer comprising on its surface a plurality of probe arrays ..."
- No "attaching the wafer to the body so that the probe arrays are exposed to the spaces of the wells"

# Alternative Designs

Patent	Alternative Designs
'243 Patent	<ul style="list-style-type: none"><li>▪ White light with filter to excite fluorescence</li><li>▪ Nanocrystals to label DNA</li><li>▪ Non-covalent attachment of DNA to bead</li></ul>
'365 Patent	<ul style="list-style-type: none"><li>▪ Non-barcode identification systems</li><li>▪ Radio frequency identification chips</li></ul>
'531 Patent	<ul style="list-style-type: none"><li>▪ One set of beads per slide</li></ul>

## Alternative Designs

- White light with filter to excite fluorescence currently used in decoding process



- Nanocrystals to label DNA has been patented by Illumina

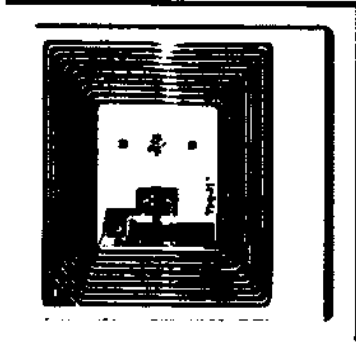


- Non-covalent attachment of DNA to bead is currently used in the GoldenGate / DASL assays

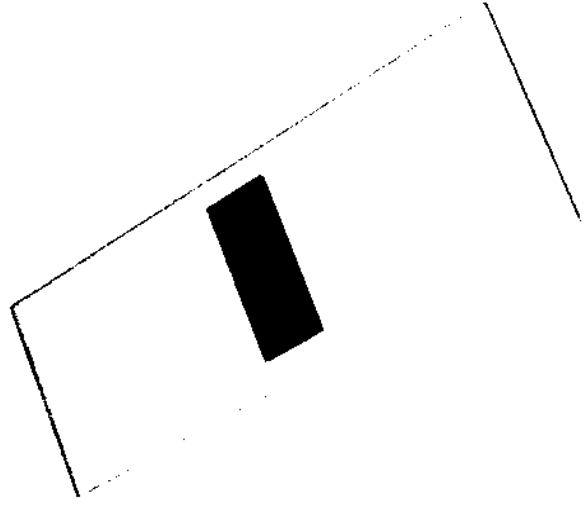


## Alternative Designs

- **Non-barcode identification systems**



- **One set of beads per slide**



# Illumina's BeadChip Does Not Have A "Wafer"

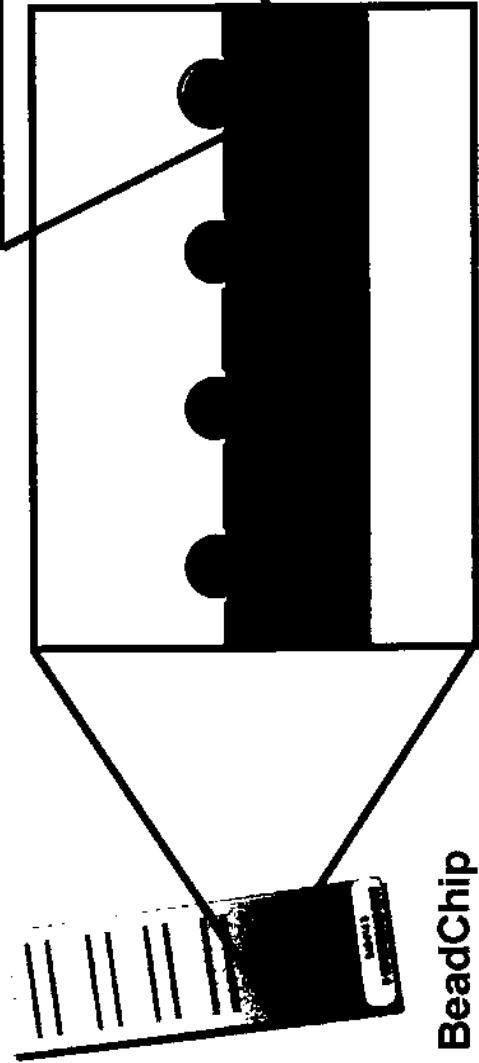
## '531 Patent, Claim 1

1. A method for making a biological chip plate comprising the steps of:

\* \* \*

(b) providing a wafer comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner;

*Claim 1, '531 Patent, col. 12:41-49*



BeadChip

# Illumina's Products Do Not Meet The Attaching Step According To Affymetrix's Own Expert

## Affymetrix's Expert

It is my opinion that the

'126 PCT application does not describe any method for attaching ...

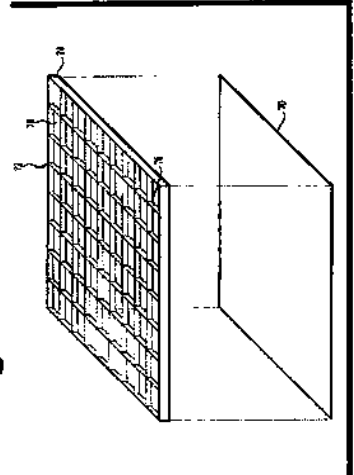
Felder Decl. ¶ 11

## Chetverin '126 Patent Application

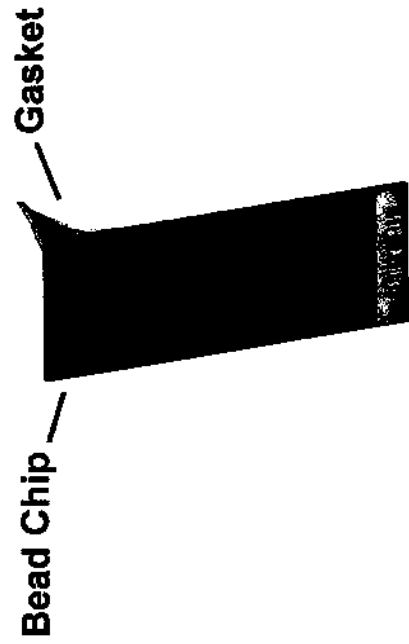
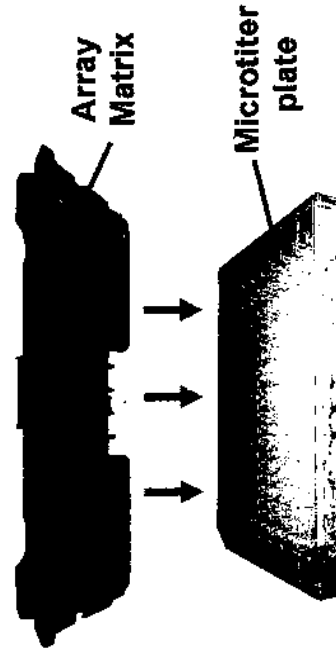
The sectioned array can also be created by applying a lattice to the solid support and bonding it to the surface so that each area is surrounded by impermeable walls. An exploded perspective view of such a sectioned array is shown in Figure 3.

WO 83/17126 at 7

Fig. 3 of '463 Patent



Illumina's Products –  
NO “attaching”



# Illumina's Products Do Not Meet The Attaching Step According To Affymetrix's Own Expert

## Affymetrix's Expert

11. The '126 PCT application also depicts, in Figure 7, a "survey array" laying on top of a "partialing array." (Exh. B at IAFP00013518). It is my opinion that the '126 PCT application does not describe any method for attaching and providing adequate contact between the "survey array" and the "partialing array," in order to allow sufficient hybridization to occur.

Felder Decl. ¶ 11

## Chetverin '126 Patent Application

The sectioned array can also be created by applying a lattice to the solid support and bonding it to the surface so that each area is surrounded by impermeable walls. An exploded perspective view of such a sectioned array is shown in Figure 3.

WO 93/17126 at 7

Fig. 3 of '126 App.

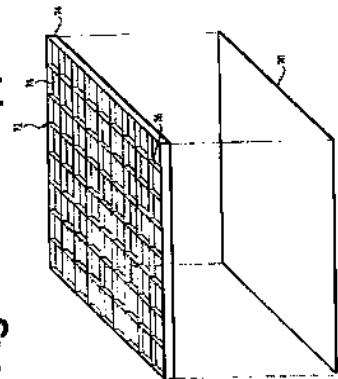
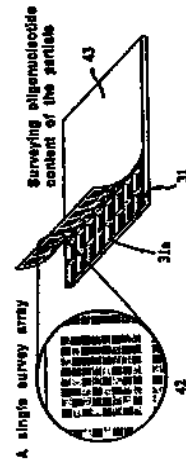
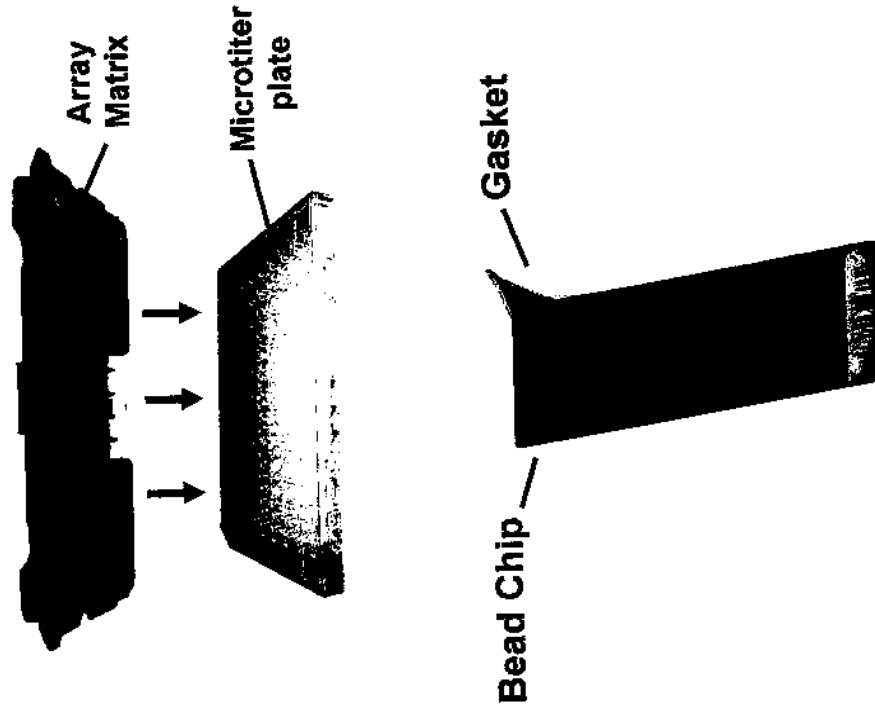


Fig. 7 of '126 App.



## Illumina's Products – NO "attaching"



# A "Wafer" Has A Single Surface

## '531 Patent

This invention contemplates a number of embodiments of the biological chip plate. In a preferred embodiment, depicted in FIG. 4, the biological chip plate includes two parts. One part is a wafer 410 that includes a plurality of biological arrays 420.

\* \* \* \* \*

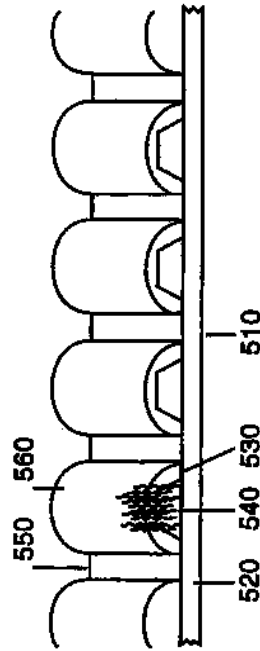
FIG. 5 depicts a cross-section of this embodiment, showing the wafer 510 having a substrate 520 (preferably transparent to light) and a surface 530 to which is attached an array of probes 540.

\* \* \* \* \*

In another embodiment, the biological chip plate has a wafer having a plurality of probe arrays and a material resistant to the flow of a liquid sample that surrounds each probe array.

'531 Patent col. 8:1-5, 8:11-14, 8:28-31

**Fig. 5**



**Fig. 6**

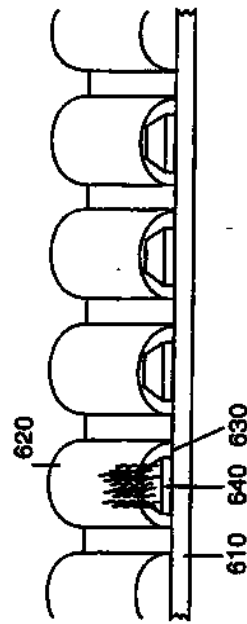


FIG. 3 depicts an example of a biological chip plate 300 used in the methods of this invention based on the standard 96-well microtiter plate in which the chips are located at the bottom of the wells. Biological chip plates include a plurality of test wells 310, each test well defining an area or space for the introduction of a sample, and each test well comprising a biological chip 320, i.e., a substrate and a surface to which an array of probes is attached, the probes being exposed to the space. FIG. 7 shows a top-down view of a well of a biological chip plate of this invention containing a biological chip on the bottom surface of the well.

\* \* \* \* \*

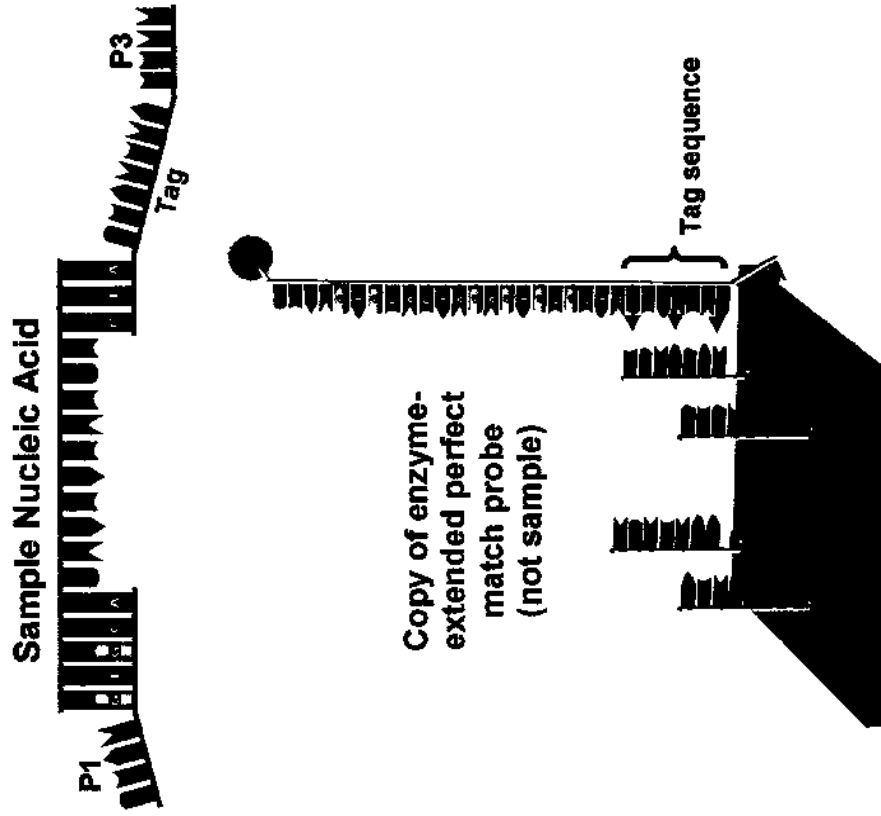
In another preferred embodiment, depicted in cross section in FIG. 6, the plates include a body 610 having preformed wells 620, usually flat-bottomed. Individual biological chips 630 are attached to the bottom of the wells so that the surface containing the array of probes 640 is exposed to the well space where the sample is to be placed.

'531 Patent col. 7:57-57, 8:22-26



# GoldenGate does not have “probe intensities”

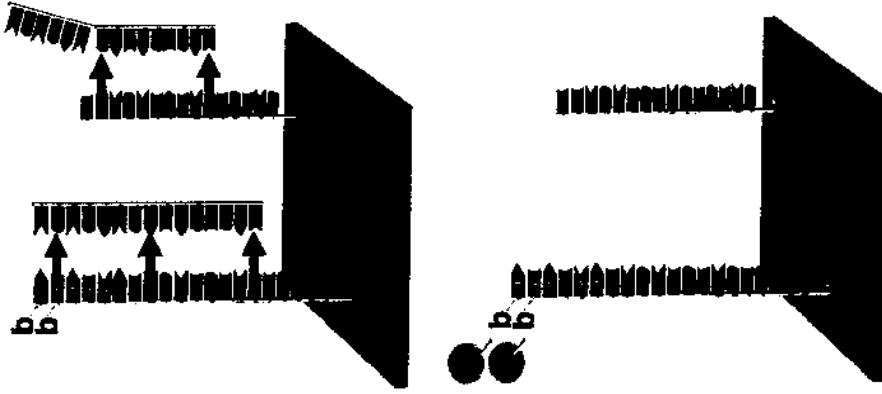
- No *labeled sample* nucleic acid
- Probes do not have a location (probe in solution)
- No probe intensity from labeled sample nucleic acid



Why are there no “probe intensities”?  
Enzymes & Tags

## Infinium does not have “probe intensities”

- No *labeled* sample nucleic acid
- Label put on *extended* probe after sample washed away



Why are there no “probe intensities”?  
Enzymes

# '716 claims require probe intensities that indicate the relative strength of binding

## Court's Construction

12. The phrase "indicating an extent of hybridization," as used in the claims of U.S. Patent No. 5,795,716, means "indicating the relative strength of binding;"

Markman Order at ¶ 12

## '716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

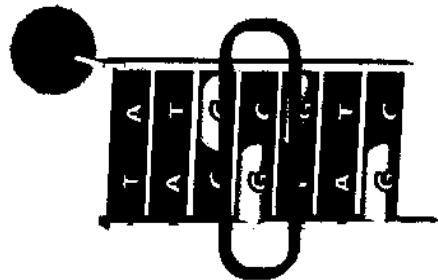
computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and

a computer readable medium that stores said computer codes.

'716 Patent col. 41:59-67; 42:59-67

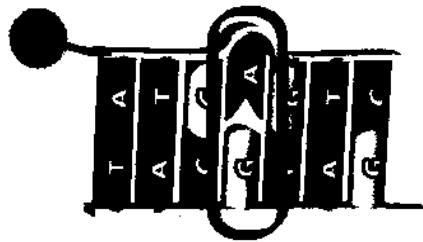
## Perfect Match



50 watts



## Mismatch



40 watts



# '716 Patent Claim 1: Applying the claim

## '716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies [REDACTED] comprising:

ing:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates [REDACTED] according to results of said comparison and said sequences of said nucleic acid probes; and  
a computer readable medium that stores said computer codes.

Base call is of an  
unknown base in a  
sample nucleic acid

'716 Patent col. 41:59-67; 42:59-67

# '716 Patent Claim 1: Applying the claim

## '716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies

an unknown base in a sample nucleic acid comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates according to results of said comparison and said sequences of said nucleic acid probes; and a computer readable medium that stores said computer codes.

Base call is of an unknown base in a sample nucleic acid

Nucleic acid probe is complementary to a sample nucleic acid

# '716 Patent Claim: "probe intensity"

## '716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and  
a computer readable medium that stores said computer codes.

Probe intensity is generated from  
a labeled sample nucleic acid

Probes have a probe location  
(usually in an array)

## Court's Construction

'716 Patent col. 41:59-67; 42:59-67

10. The term "probe intensity," as used in the claims of U.S. Patent No. 5,795,716, means "intensity from a labeled sample nucleic acid hybridized to a [REDACTED]"

Merkman Order at ¶ 10

# '716 Patent Claim: "probe intensity"

## '716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and  
a computer readable medium that stores said computer codes.

Labeled sample nucleic acid  
must have unknown base to be  
determined

'716 Patent col. 41:59-67; 42:59-67

## Court's Construction

10. The term "probe intensity," as used in the claims of U.S. Patent No. 5,795,716, means "intensity from a labeled sample nucleic acid hybridized to a probe location;"

Markman Order at ¶ 10

# '716 Patent Claim: "probe intensity"

## '716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

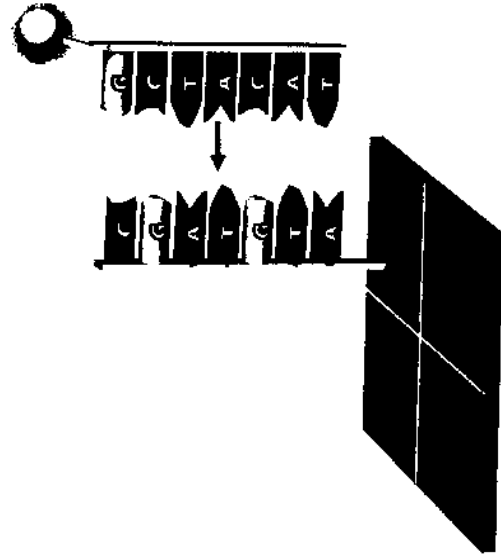
computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and  
a computer readable medium that stores said computer codes.

Labeled sample nucleic acid must have unknown base to be determined

Labeled sample hybridizes to probe at probe location



## Court's Construction

'716 Patent col. 41:59-67; 42:59-67

10. The term "probe intensity," as used in the claims of U.S. Patent No. 5,795,716, means "intensity from a labeled sample nucleic acid hybridized to a probe location;"

Markman Order at ¶ 10

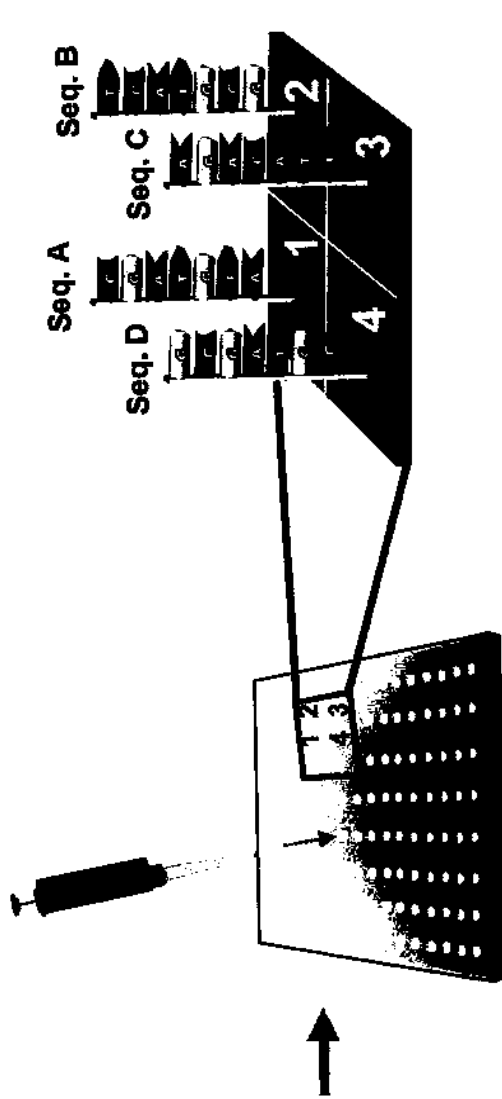


# Accused Arrays Not “Deposited”

## Array by Deposition

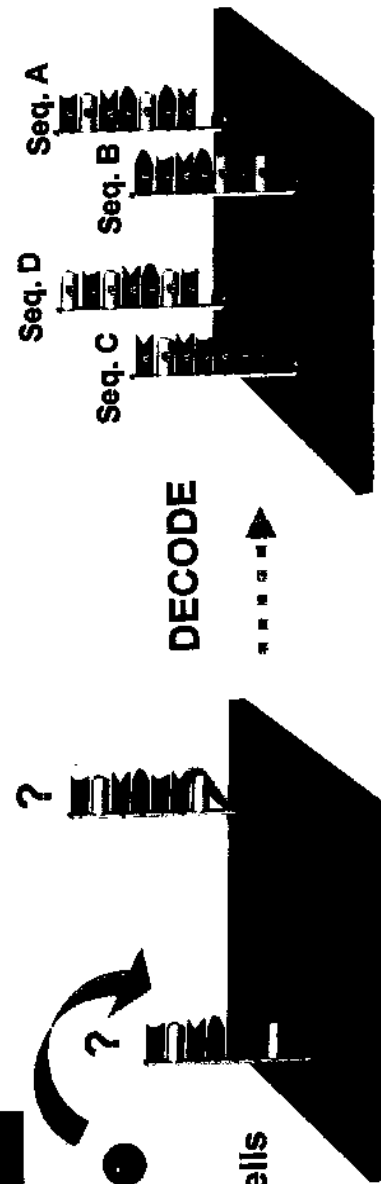
<b>Position</b>	<b>Sequence</b>
<b>1</b>	<b>Seq. A</b>
<b>2</b>	<b>Seq. B</b>
<b>3</b>	<b>Seq. C</b>
<b>4</b>	<b>Seq. D</b>

### DNA made then deposited on array at known locations

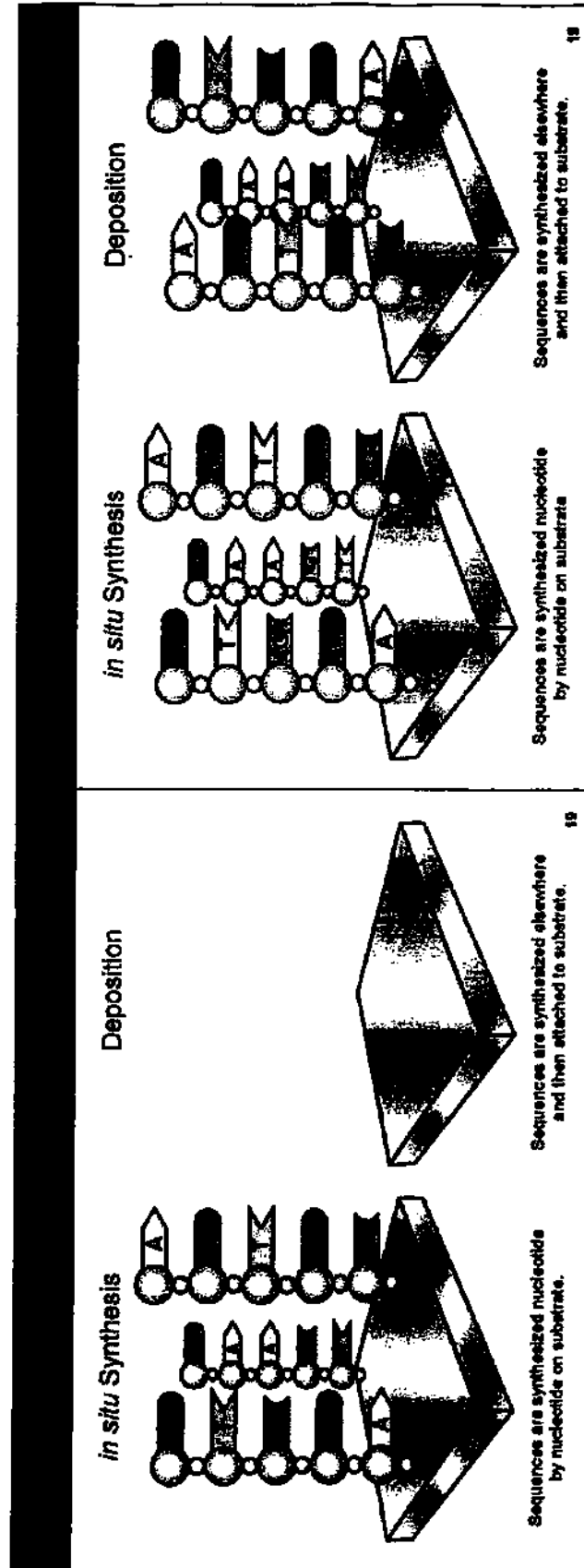


## Ilumina's Random Array

### DNA made on beads and randomly assembled into wells

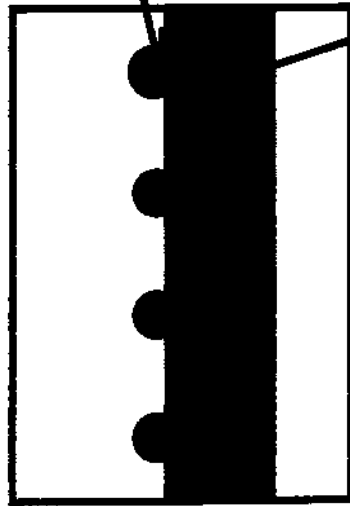


# Deposition Of Arrays Defined By Affymetrix

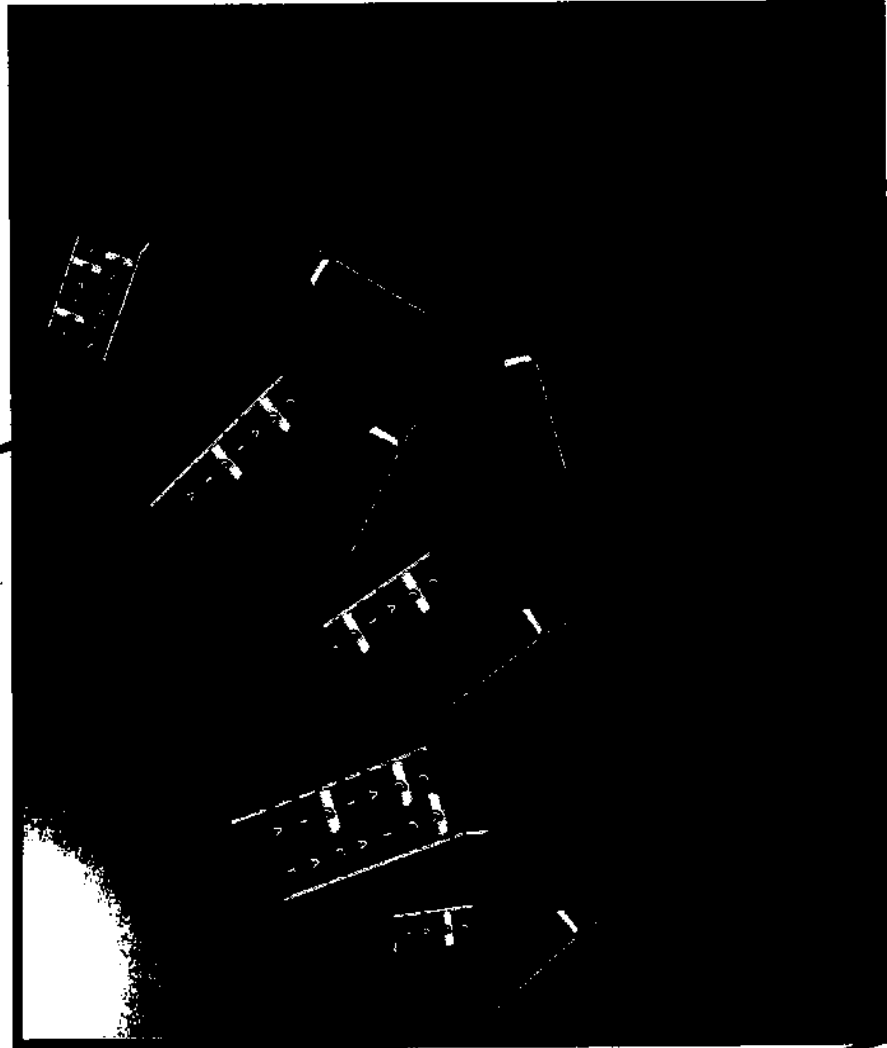


Affymetrix Markman Hearing Slide 19

# Entire Bead Surface Accessible For Chemical Reactions



Bead Surface



# '365 Patent Not Infringed

Asserted Claims	[Insert Accused Products and Methods]
Claim 36	<ul style="list-style-type: none"><li>▪ No "probe array deposited on a substrate"</li><li>▪ No "... biological polymers immobilized on said substrate"</li><li>▪ No "... having a density exceeding 1000 different nucleic acids per cm<sup>2</sup>"</li></ul>
Claim 41	<ul style="list-style-type: none"><li>▪ No "... biological polymers immobilized on said substrate"</li><li>▪ No "... having a density exceeding 1000 different nucleic acids per cm<sup>2</sup>"</li></ul>

# GoldenGate/DASL Do Not Have "Biological Polymers Immobilized On A Surface"

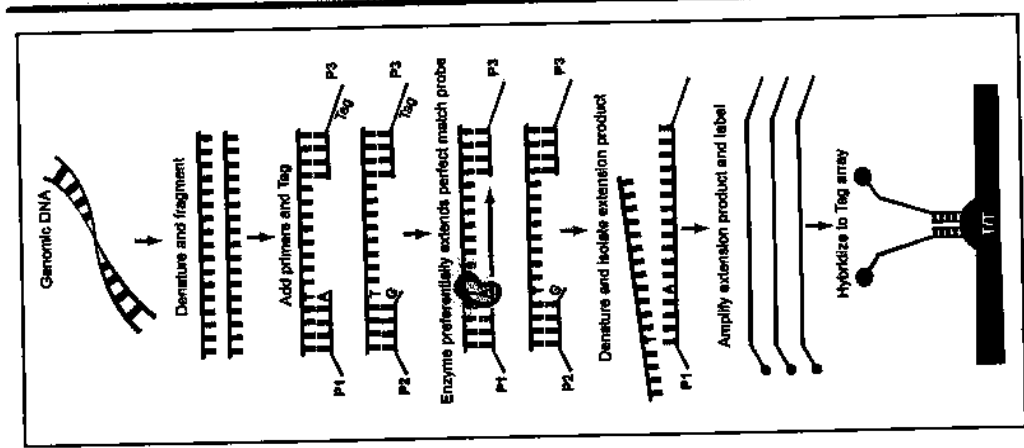
## Court's Construction

7. The phrase "biological polymers immobilized on a surface," as used in the claims of U.S. Patent No. 6,399,365, means "two or more surface-immobilized biological polymers that are recognized by a particular target;"

Markman Order at ¶ 7

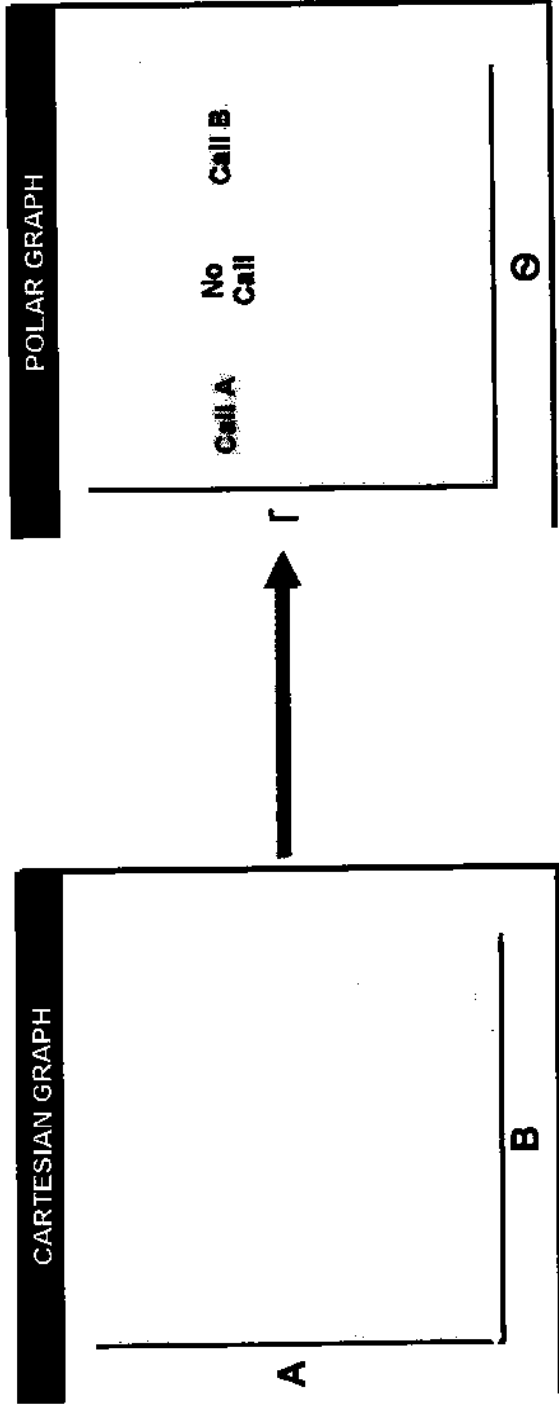
[Insert Trial Testimony Here]

## GoldenGate/DASL

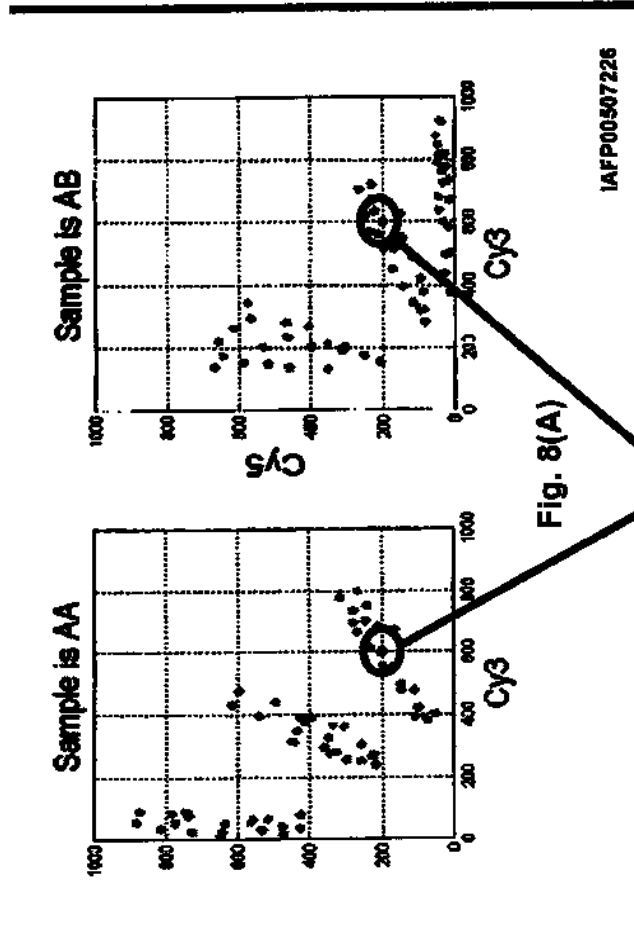
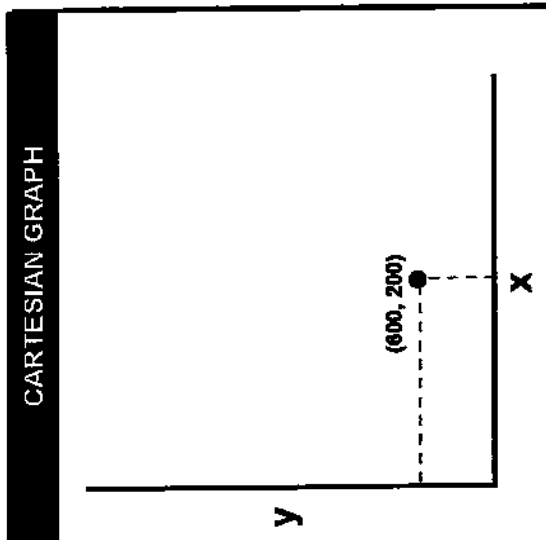


# '716 patent: "comparison of probe intensities to each other"

- If  $A \gg B$  – Call A
- If  $B \gg A$  – Call B
- If  $A \sim B$  – No Call



**GenCall does not make a base call based on comparing probe intensities to each other**

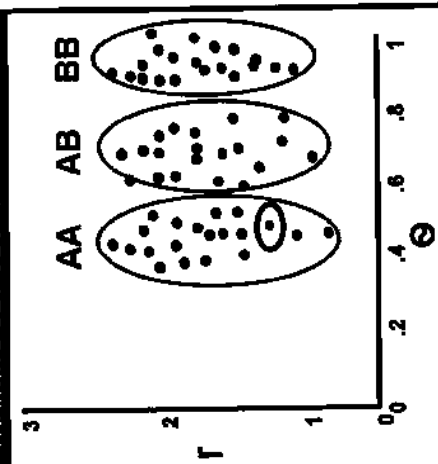


**If “compared to each other,” Sample AA and Sample AB have identical intensities**

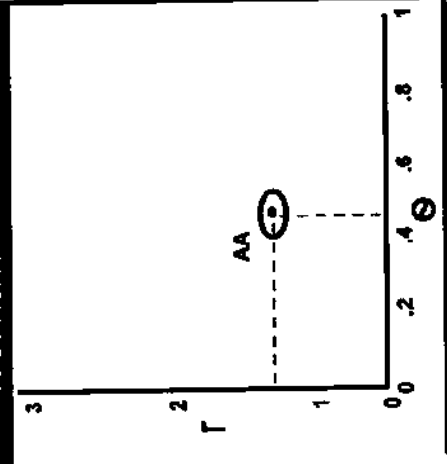
GenCall does not make a base call based on comparing probe intensities to each other

## SAMPLE AA

TRAINING SET CLUSTERS LOCUS 1

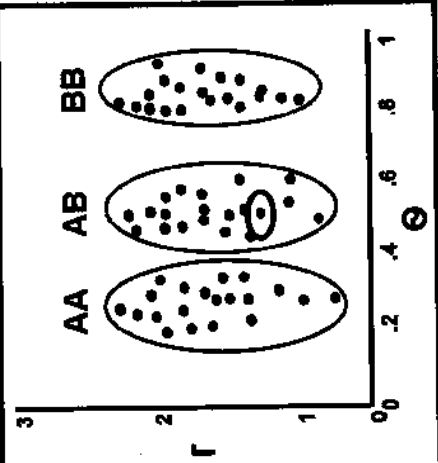


PLOT AGAINST CLUSTERS

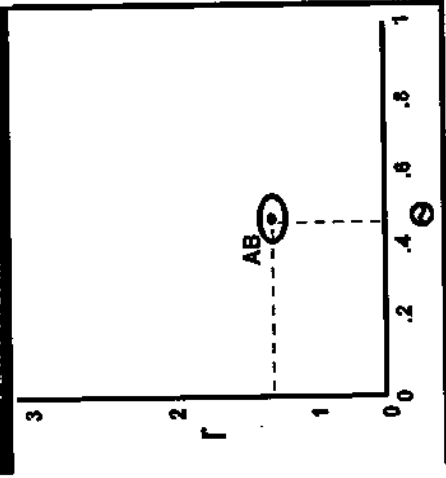


## SAMPLE AB

TRAINING SET CLUSTERS LOCUS 2

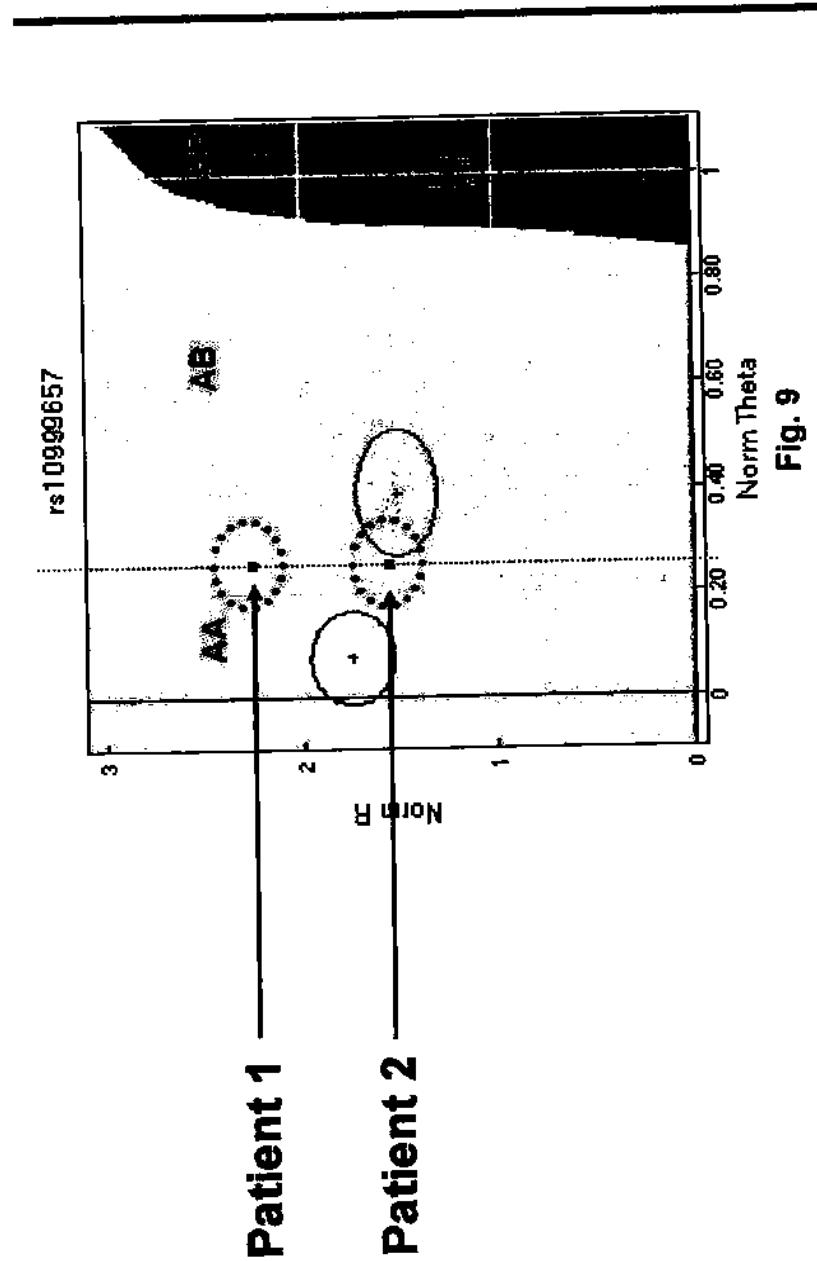


PLOT AGAINST CLUSTERS





**GenCall does not make a base call based on comparing probe intensities to each other**



Quackenbush Rebuttal Report pg. 42

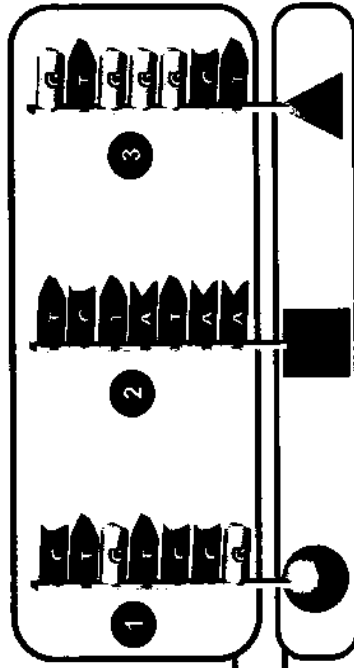
**Data from Patient 1 and Patient 2 have same angle  
(i.e., same comparison to each other)  
but *different* genotypes**

# No "Different Beads" Having Different Nucleic Acids

## '243 Patent Claim 35

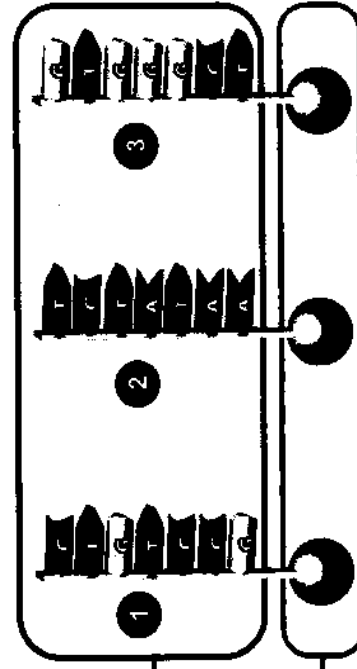
providing a substrate having an array of at least 1000  
 nucleic acids, the array occupying an area  
 on a substrate of less than 1 cm<sup>2</sup>, at least some of the  
 nucleic acids having  
 covalently attached thereto;

Claim 35, '243 Patent, col. 31:62 - 32:13



## Accused Methods

- Different nucleic acids
- NOT "different" beads

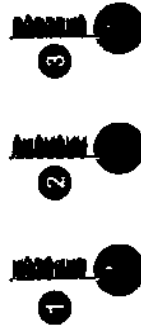


# Beads Not Different Due To Different Nucleic Acids

## Affymetrix Argument

### Claim 35

...at least some of the different beads having different nucleic acids covalently attached thereto; '243 Patent, col. 31:67-32:1



=

~~different~~ beads having different nucleic acids covalently attached thereto; ...at least some of the



## Correct Reading

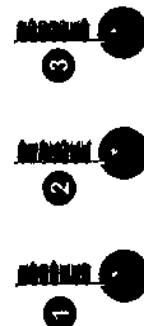
### Claim 35

...at least some of the different beads having different nucleic acids covalently attached thereto; '243 Patent, col. 31:67-32:1

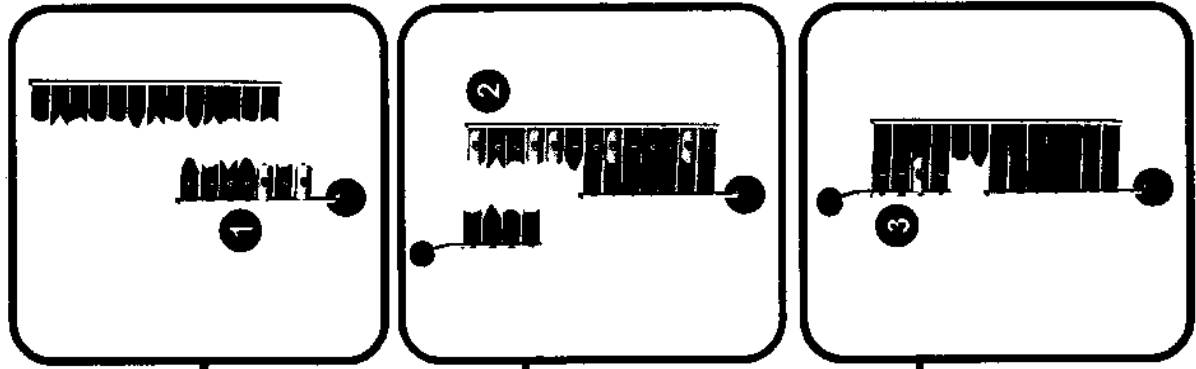


#

~~different~~ beads having different nucleic acids covalently attached thereto; ...at least some of the



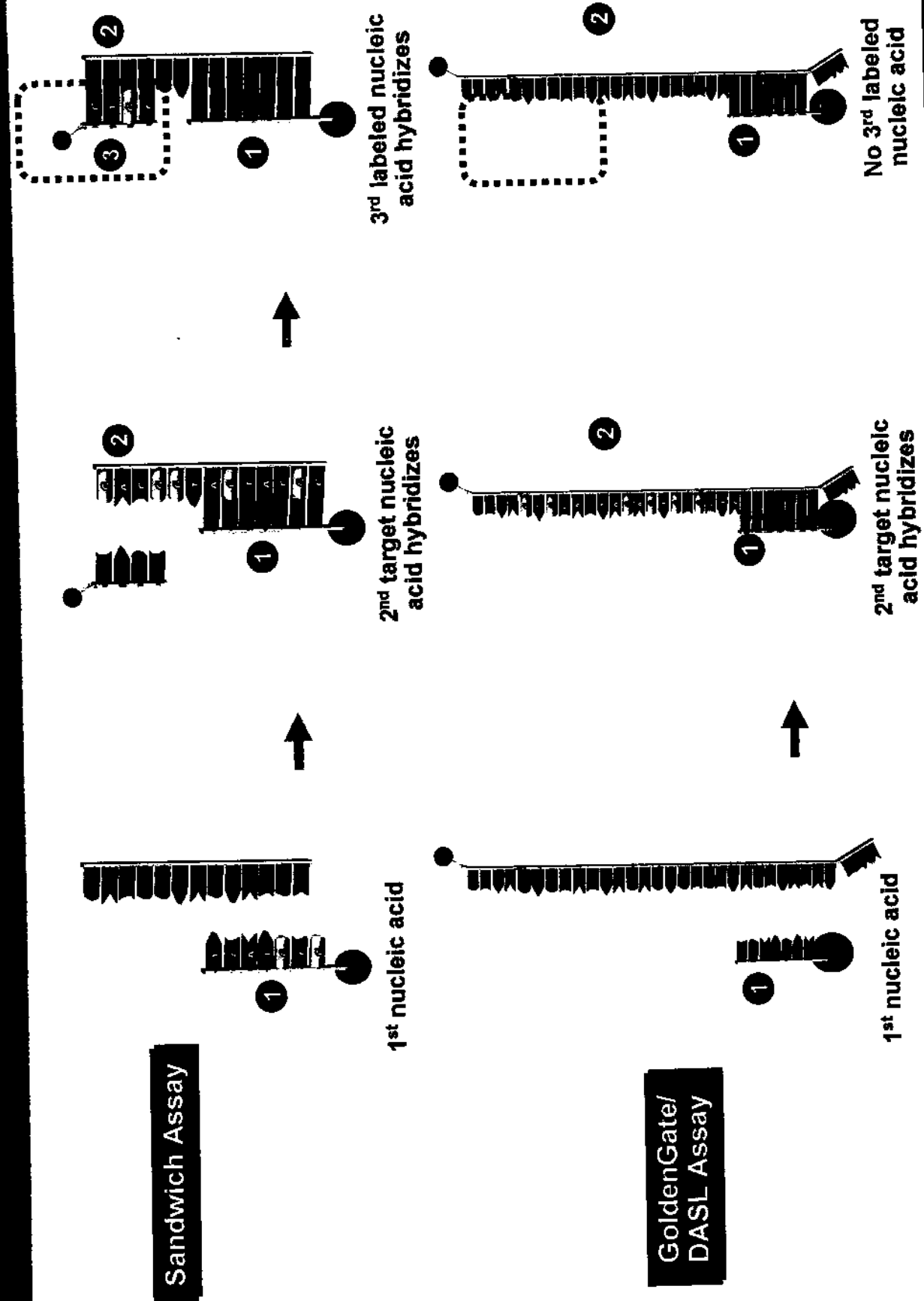
# Claim 35 Describes A Sandwich Assay



contacting the target nucleic acids and the beads so that  
after contact

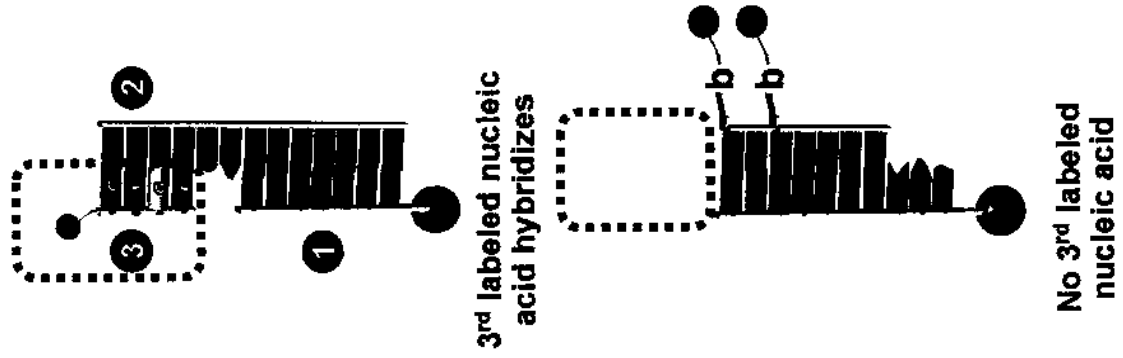
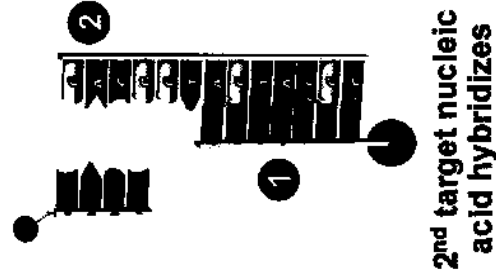
'243 Patent, col. 31:62 - 32:13

# Illumina's GoldenGate/DASL Are Not Sandwich Assays

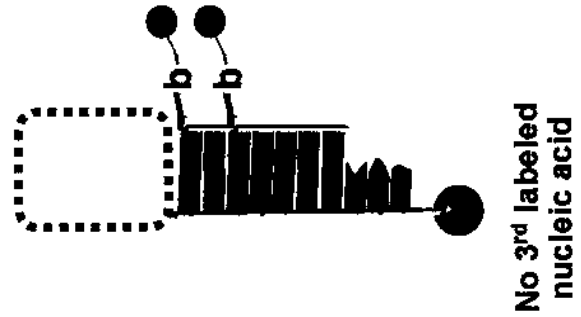
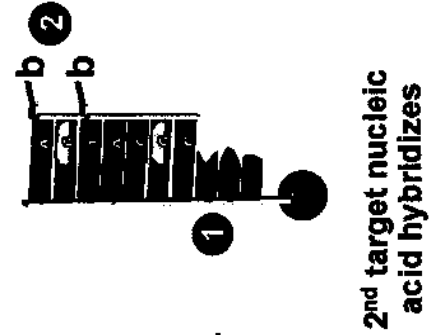
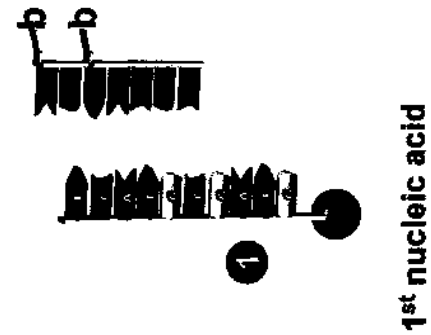


# Illumina's Direct Hyb Is Not A Sandwich Assay

## Sandwich Assay

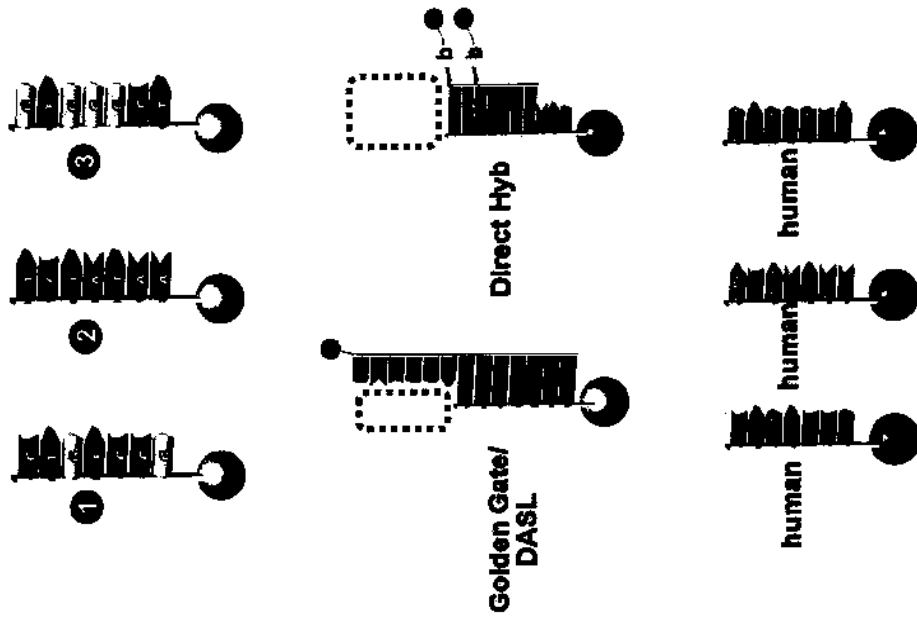


## Direct Hyb Assay



# Illumina Does Not Infringe The '243 Patent

- No “different” beads (claims 14, 15, 35)
- Not a sandwich assay (claims 35)
- No different species of nucleic acids (claims 14, 15)



# Illumina Does Not Infringe The '243 Patent

Asserted Claims	Accused Products/Methods
Claim 14	<ul style="list-style-type: none"><li>▪ No “different beads”</li><li>▪ No “different species”</li></ul>
Claim 15	
Claim 35	<ul style="list-style-type: none"><li>▪ No “different beads”</li><li>▪ Not a sandwich assay</li></ul>



# Illumina Does Not Infringe The '243 Patent

<b>Claim Requirements</b>	<b>Golden Gate/ DASL System</b>	<b>Direct Hyb System</b>
<b>Different Beads</b> (claims 14, 15, 35)	<b>Beads are the same</b>	<b>Beads are the same</b>
<b>Different Species of Nucleic Acids</b> (claims 14, 15)	<b>No "different species" of nucleic acids</b>	<b>No "different species" of nucleic acids</b>
<b>Sandwich Assay</b> (claims 35)	<b>Not a sandwich assay</b>	<b>Not a sandwich assay</b>

# Different Beads Cannot Be Distinguished By The Sequence Attached

## Claim 35

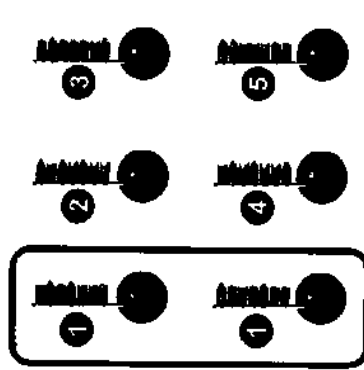
... at least some of the different beads having different nucleic acids covalently attached thereto; '243 Patent, col. 31:67-32:1

### Affymetrix Argument

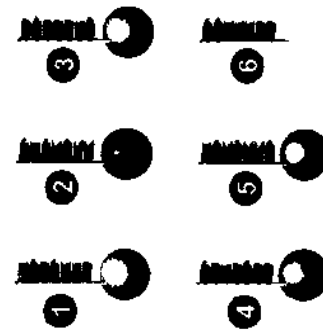
Only difference between beads is different nucleic acids attached



Some of the different beads having the same nucleic acids



Not "different" beads



"Different beads having different nucleic acids" attached

### Correct Reading



"Different" beads

# Illumina's Array Matrix And BeadChip Do Not Have A Single Surface

## Court's Claim Construction

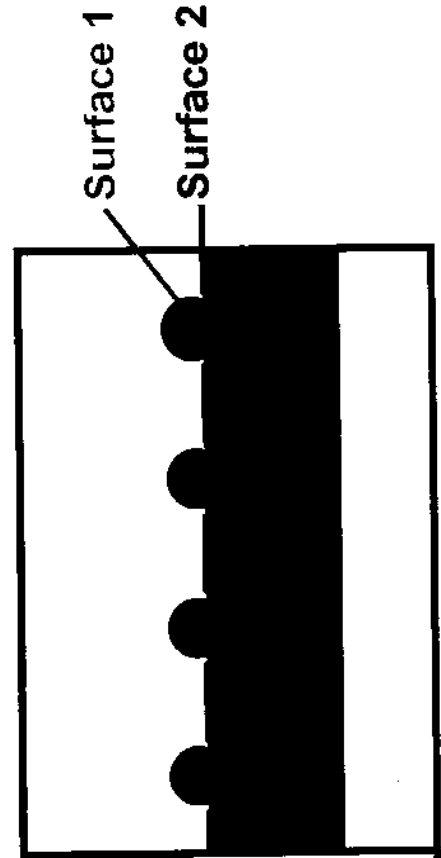
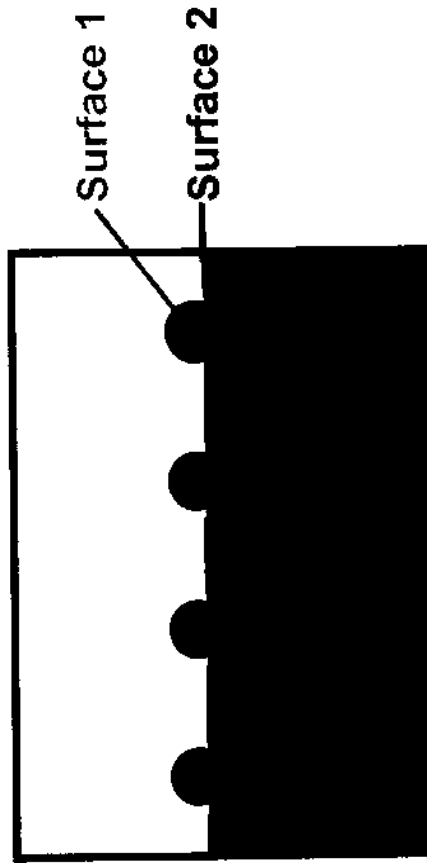
The term "Substrate," as used in the claims of U.S. Patent No. 6,646,243, means "a material having a rigid or semi-rigid surface;"

Markman Order, ¶ 3.

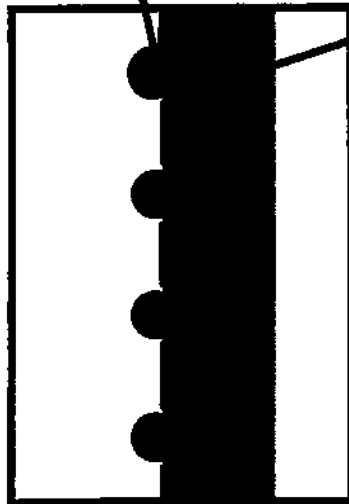
### SAM underside



### BeadChip



# Each Bead's Surface Is Separate From The Well Surface



**Entire bead surface is accessible**



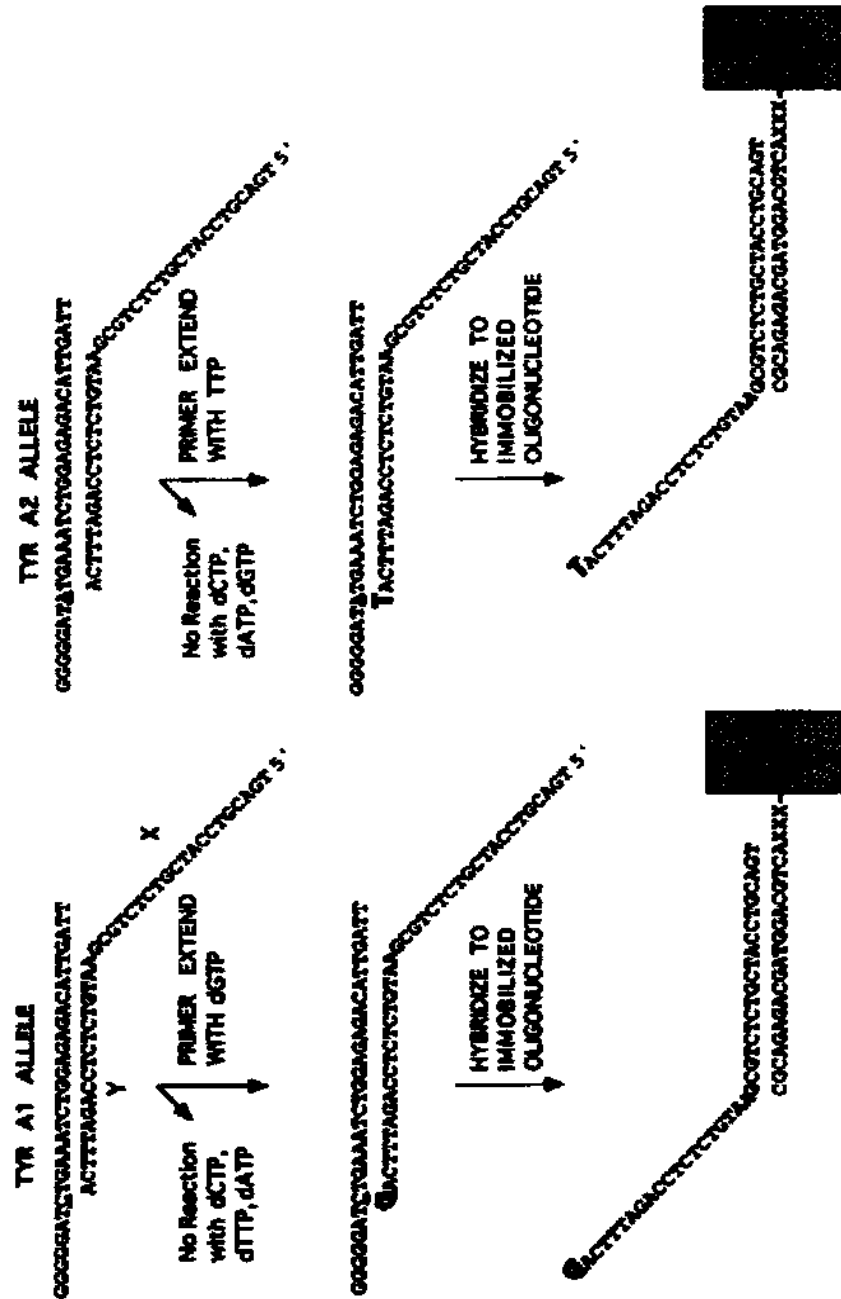
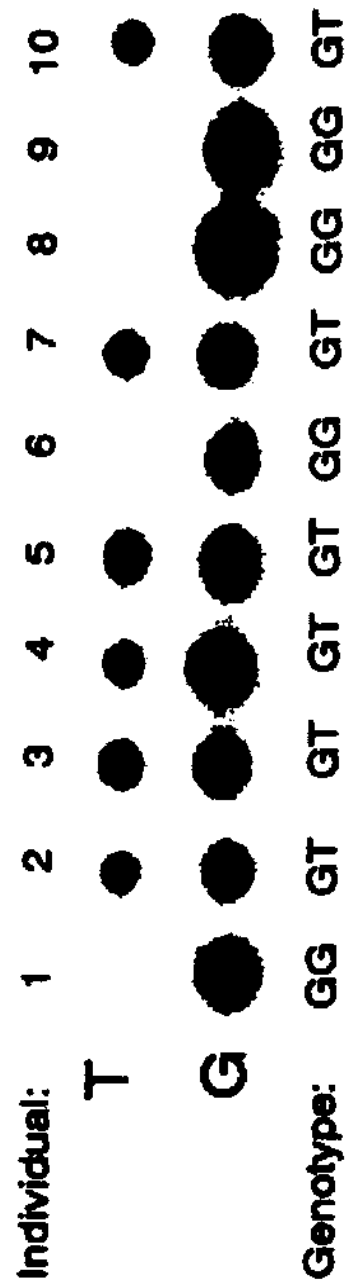


Figure 1. A schematic description of the AS-PE-capture method for the detection of alleles of the human TYR locus. T or G labeled using  $\alpha$ - $^{32}$ P TTP and  $\alpha$ - $^{32}$ P dGTP, respectively.

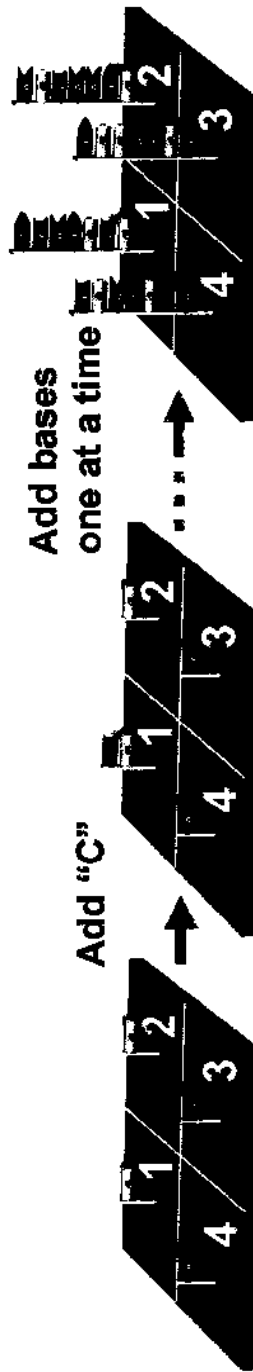


**Figure 2.** Hybridization of the AS-PE products to immobilized 3' amino-oligonucleotide. DNA from 10 individuals was amplified with TYR 1 and TYR 2 primers (Table 1) and the amplification products subjected to the AS-PE-capture method.

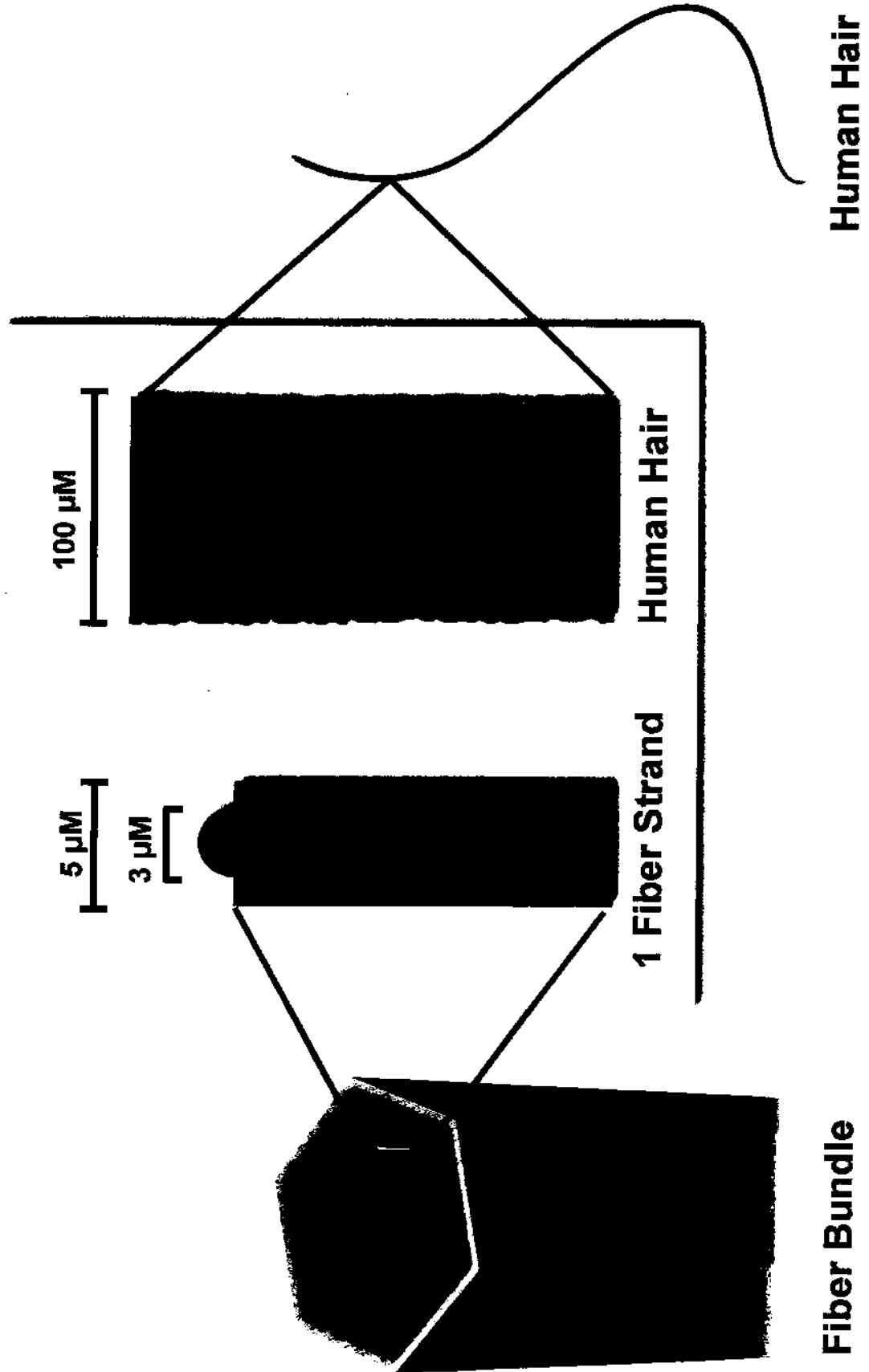
# ***“In Situ” Array***

## **Probe Set #1**

<u>Position</u>	<u>Sequence</u>
1	GCGTACT
2	GTAACGA
3	CGTAGGT
4	ATGTAGC

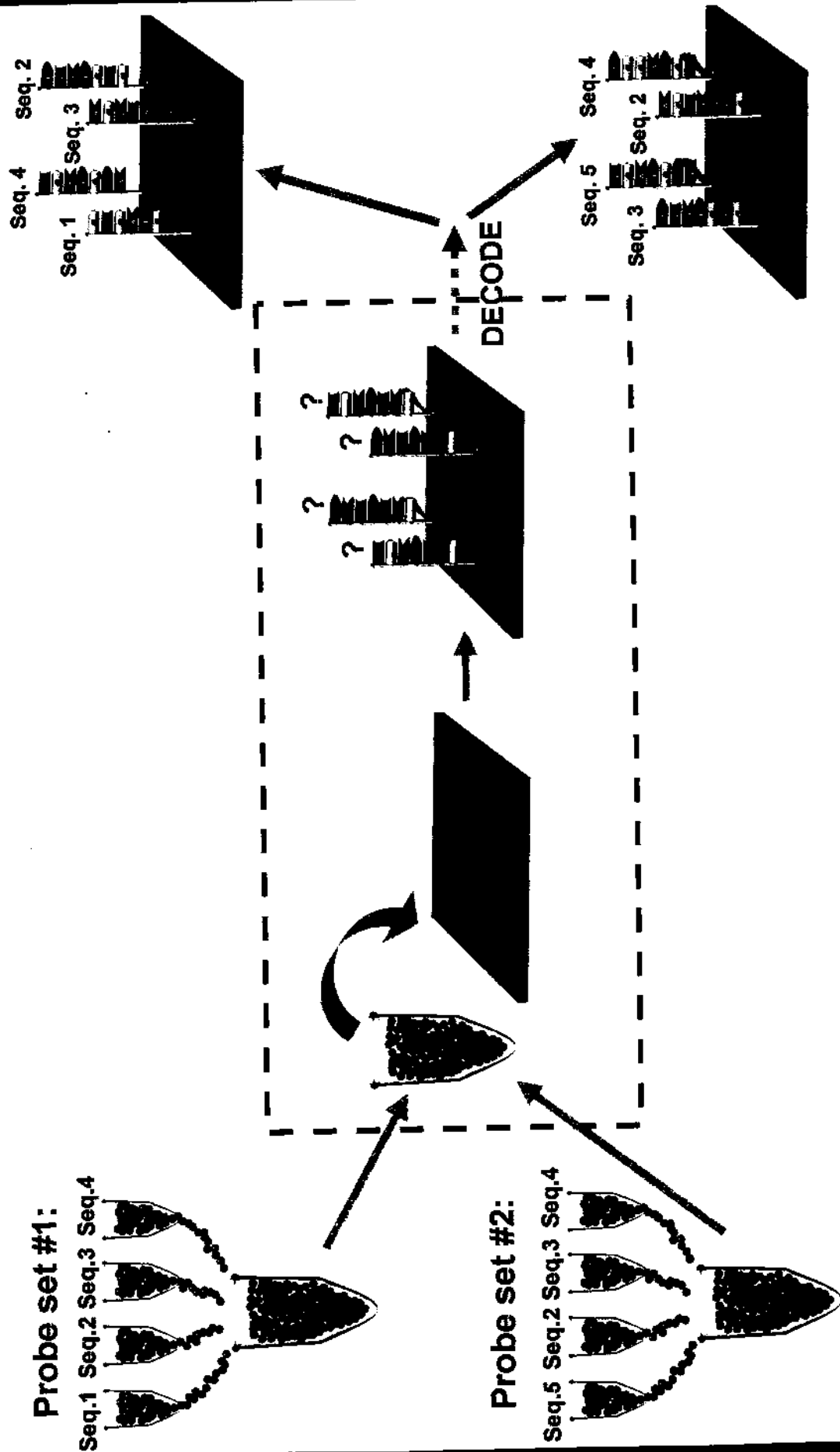


# Beads Used In Illumina's Arrays

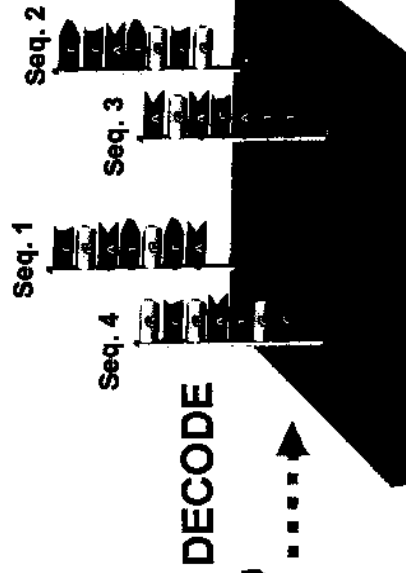
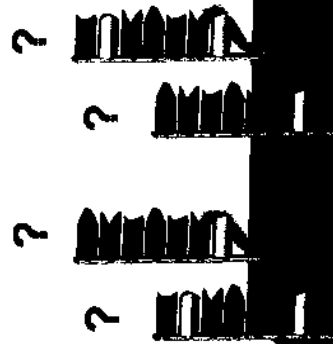
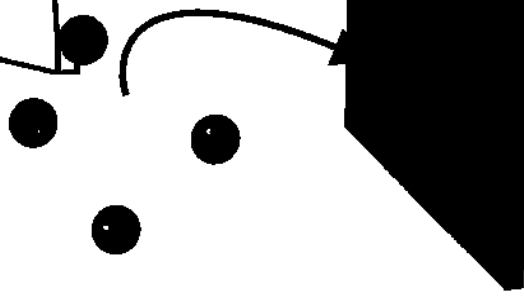




# Flexibility Of Manufacturing



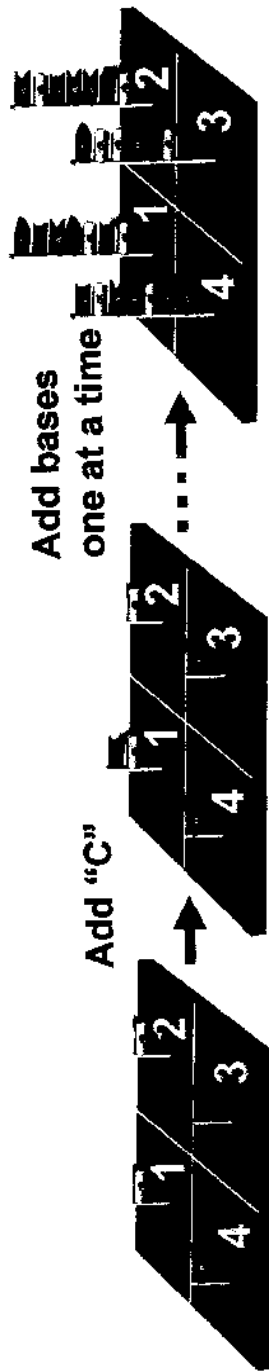
# Illumina's Random Arrays



# In Situ Arrays Lack Flexibility

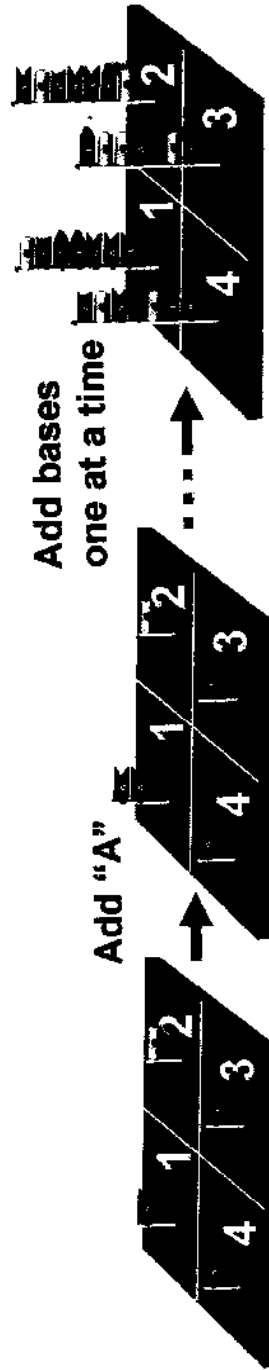
## Probe Set #1

Position	Sequence
1	GCGTACT
2	GTAACGA
3	CGTAGGT
4	ATGTAGC



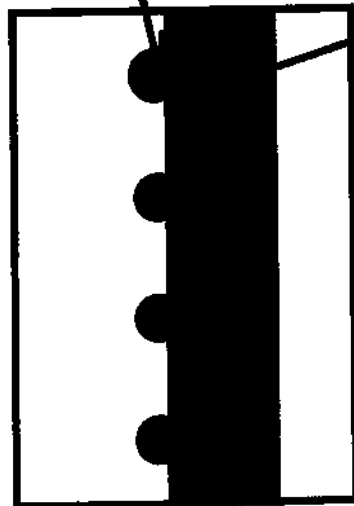
## Probe Set #2

Position	Sequence
1	AAATTCCG
2	GTAACGA
3	CGTAGGT
4	ATGTAGC



Change in DNA content requires changing manufacturing steps

# Entire Bead Surface Accessible For Chemical Reactions

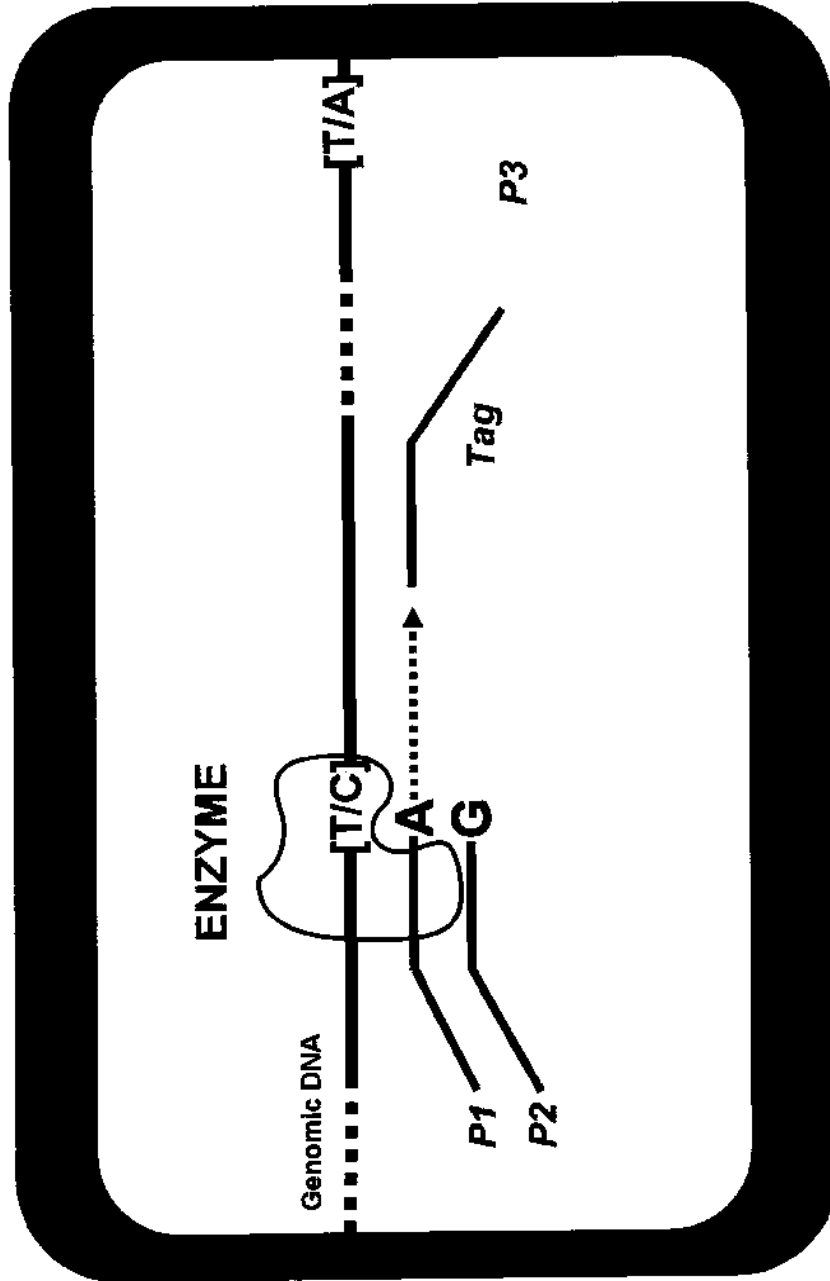


Bead Surface

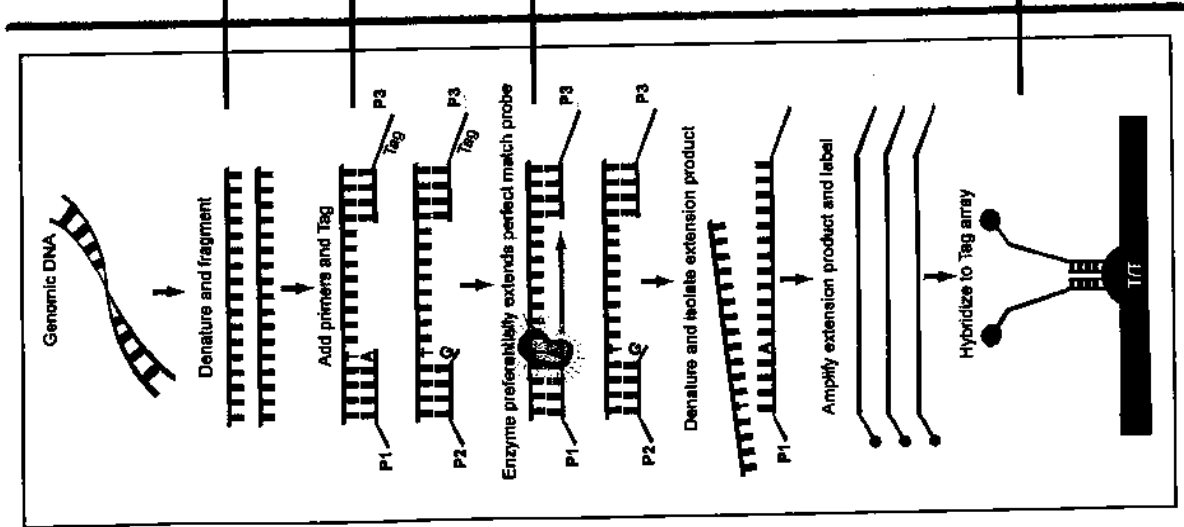


# GoldenGate Assay

## ALLELE SPECIFIC EXTENSION

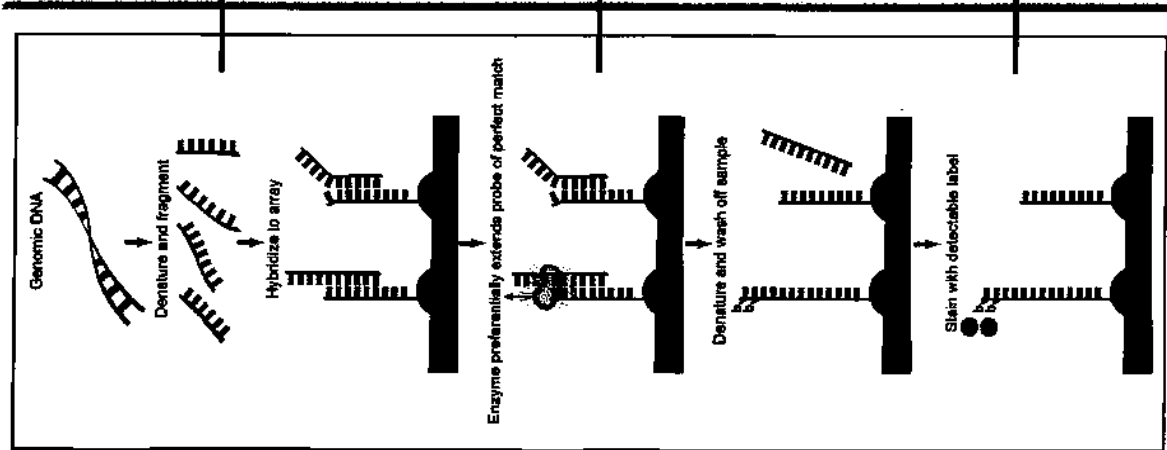


# Illumina's GoldenGate does not infringe the '716 patent



- **No *labeled* sample nucleic acid**  
(sample is *never* labeled)
- **No probe location**  
(probe in solution)
- **No probe intensity indicating relative strength of binding**  
(intensity indicates preferential extension by enzyme)
- **No intensity from labeled sample nucleic acid hybridized to probe location** (only tag of enzyme-extended probe bound to address)

# Illumina's Infinium does not infringe the '716 patent



■ **No labeled sample nucleic acid**  
(sample is *never* labeled)

■ **No probe intensity indicating relative strength of binding**  
(intensity indicates preferential extension by enzyme)

■ **No intensity from labeled sample nucleic acid hybridized to probe location** (label only on enzyme-extended probe)

# '716 Patent Claim 1 v. Claim 5

## '716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and  
a computer readable medium that stores said computer codes.

'716 Patent col. 41:89-97; 42:89-97

## '716 Patent Claim 5

5. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other; and  
computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes.

'716 Patent col. 43:86-97; 44:1-18



# GoldenGate does not have an “array of probes” of claim 9

Probes are complementary to a  
labeled sample nucleic acid

GoldenGate does not have array of  
probes that are complementary to  
a labeled sample nucleic acid

’716 Patent Claim 9

9. A system according to claims 5, 6, 7, or 8, wherein the plurality of nucleic acid probes are in an array of probes.

’716 Patent Claim 5

5. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:  
a processor; and  
a computer readable medium coupled to said processor for storing a computer program comprising:  
computer code that receives a plurality of signals

hybridization of a nucleic acid probe  
with at least one nucleic acid sequence including said  
sample sequence,

computer code that performs a comparison of said plurality of probe intensities to each other; and  
computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes.

GoldenGate  
Assay

